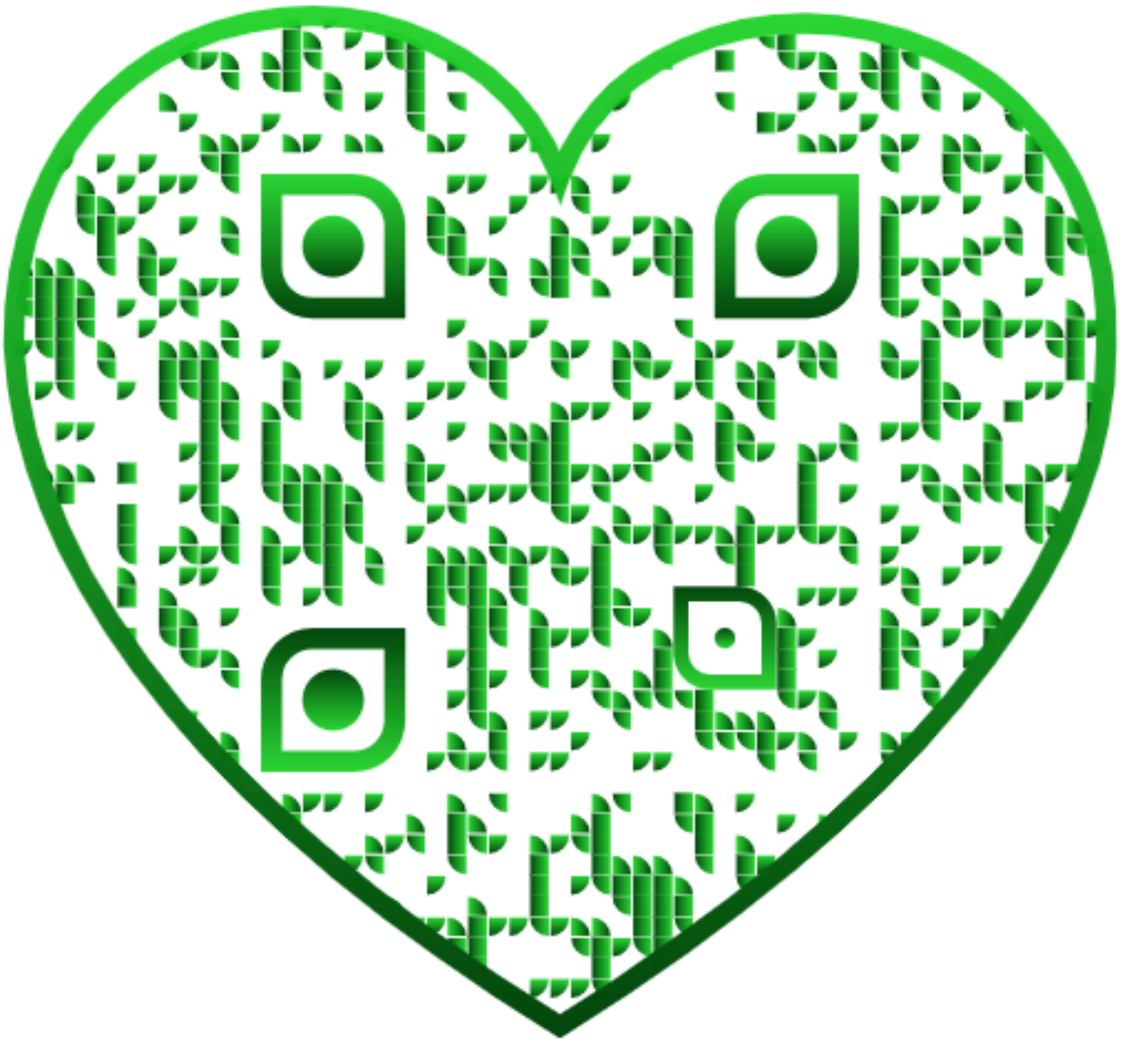
5. Packaging and storage of pharmaceuticals



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- Packaging is the **science**, **art**, and **technology** of enclosing or protecting products for distribution, storage, sale, and use.
- Packaging also refers to the process of design, evaluation, and production of packages.
- Defined functions of packages - Presentation, Identification, Protection, Convenience, Containment during storage, Compliance, Integrity and Stability of the product.
- Packaging is a critical tool in the pharmaceutical industry for product delivery and regulatory compliance.

- The selection of a package considers -
  - Determination of the product's physical and chemical characteristics,
  - Its protective needs, and
  - Its marketing requirements.

- Factors influencing choice of pack -
    - The product
    - The market
    - The distribution system
    - Manufacturing facilities

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Purposes of packaging

- Physical protection
  - Mechanical shock, vibration, electrostatic discharge, compression, and temperature
- Barrier protection
  - A barrier from oxygen, water vapor, dust, etc.

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- Containment or agglomeration
  - Small objects are typically grouped together in one package for reasons of efficiency.
- Information transmission
  - Packages and labels communicate how to use, transport, recycle, or dispose of the package or product.
- Marketing
  - Package graphic design and physical design will encourage buyers to purchase the product.

- Security
  - Packages can be made with improved tamper resistance to deter tampering and also can have tamper-evident features to help indicate tampering.
- Anti-counterfeit Packaging
  - Packages can be engineered to help reduce the risks of package pilferage or the theft and resale of products
- Convenience

Packaging types

- The term ‘pack’ covers all the components involved the components enable the product to be stored, transported and displayed, and possibly assist use.
- Packages can be **generally** categorized into:
    - Primary Packages
    - Secondary Packages
    - Tertiary Packages

1. Primary Packaging

- Refers to the package that holds the product, and has the most direct contact with the actual contents.
- This usually is the smallest unit of distribution or use.
- This also applies to the closure which is also part of the primary pack.
- Should support use of the product by the patient.

2. Secondary Packaging

- The container that holds the primary packaging.
- Used to group primary packages together.
- Help to improve the appearance of the product.
- Can supply information about the product and its use.
- Should provide evidence of tampering with the medicine.

3. Tertiary packaging

- Used for shipping, bulk handling and warehouse storage.
- This is not commonly displayed on the retail shelf.

- Based on packaging **forms**:
  - Blister packaging
  - Strip Packaging
  - Bubble pack
  - Shrink seals and bands
  - Pouches
  - Bottles
  - Tape seals
  - Tubes
  - Cartons

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- Based on their **utility**:
  - **Well – closed containers:** A well-closed container protects the contents from loss during transportation, handling, storage or sale.
  - **Single dose containers:** These containers are used to supply only one of medicament and hold generally parenteral products.

E.g. Ampoules

- **Multi dose containers:** These containers allow the withdrawal of dose at various intervals without changing the strength, quality or purity of remaining portion.

  E.g. vials

- **Light-resistant containers:** These containers protect the medicament from harmful effects of light.

- These containers are used to store those medicaments which are photo-sensitive.

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- **Air-tight containers:** These are also called **hermetic** containers.
  - These containers have air-tight sealing or closing.
  - These containers protect the products from dust, moisture and air.

- **Aerosol containers:** These containers are used to hold aerosol products.

  - These containers have adequate mechanical strength in order to bear the pressure of aerosol packing.

Packaging Materials

- Packaging materials must have the following **characteristics**:
  - They must protect the preparation from environmental conditions.
  - They must not be reactive with the product.
  - They must not impart to the product tastes or odors.

- Must be non toxic.
- They must meet applicable tamper – resistance requirements.
- They must be adaptable to commonly employed high-speed packaging equipment.
- It should withstand wear and tear during normal handling.

Glass Containers

- Glass is commonly used in pharmaceutical packaging because:
  - Possesses superior protective qualities
  - Economical
  - Variety of sizes and shapes
  - Essentially chemically inert

- Impermeable
- Strong
- Rigid
- Does not deteriorate with age
- Excellent barrier

- Limitation of glass containers:
  - Fragility
  - Heavy weight
  - Leaching, and
  - Flecking

- Composition of glass
  - Sand (silicon dioxide)
  - Soda ash (sodium carbonate)
  - Limestone (calcium carbonate)
  - Cullet (broken glass) – act as a fusion agent
  - Cation - aluminium, boron, potassium, magnesium, zinc, barium,
  - Anion - Oxygen

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- The composition of glass varies and can be adjusted for a specific purpose.
  - Reduction in the composition of sodium ion makes the glass chemically resistant.
  - Boron oxide is incorporated to aid melting process.
  - Lead provides clarity and brilliance, but makes the glass relatively soft.
  - Alumina (Aluminum oxide) is incorporated to increase hardness and durability.

- Colored glasses
  - May be obtained by solution or by colloidal dispersion.
  - For pharmaceutical packaging – **flint** or **amber** colored
  - Special colors can be used for decorative purposes
  - Light protection – only amber or red glasses

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- Materials added to give a glass a particular color;
  - **Amber**: Carbon and Sulphur or Iron and Manganese dioxide
  - Yellow: Compounds of cadmium and Sulphur
  - Blue: Cobalt oxide or occasionally copper (cupric) oxide
  - Green: Iron oxide, manganese dioxide and chromium dioxide
  - Opal: Involves fluorides or phosphates

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- Glasses can be manufactured either by the following processes:
  - Blowing
  - Drawing
  - Pressing and
  - Casting

- **Types** of glass (Glasses for drugs)
  - Type I – Borosilicate glass
    - Highly resistant glass
    - The alkali and earth cations are replaced by boron and/or aluminum and zinc
    - Chemically inert than the soda-lime glass
    - Significant interaction with water (Na+ can easily be leached from the glass surface)

- Type II – Treated Soda-lime glass
  - Surface treated with commercial soda-lime that has been de-alkalinized or treated to remove surface alkali
  - Sulfur treatment neutralizes the alkali oxides on the surface, thereby rendering the glass more chemically resistant.
- Type III – Regular Soda-lime glass
  - Soda glass of limited alkalinity
- NP (European Type IV) – General purpose Soda-lime glass

- **Evaluation** of glass container
  - Thermal shock test
  - Internal bursting pressure test
  - Annealing test
  - Vertical load test
  - Leakage tests
  - Autoclaving test
  - Limit test for alkalinity (Water attack test)
  - Product and pack compatibility test
  - Measurement of wall and base thickness
  - Other tests: - Formal stability test with products, light transmission test, arsenic test

Plastic Containers

- Plastics in package have proved useful for a number of reasons:
  - Ease of formation
  - High quality
  - Freedom of design
  - Resistance to breakage

- Limitations:
  - Possible extraction, interaction
  - Adsorption and absorption
  - Permeable to moisture, oxygen
  - Poor printing

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- Plastic container for pharmaceutical products are primarily made from:
  - Polyethylene (PE), Polypropylene (PP), Polyvinylchloride (PVC), Polystyrene, and to a lesser extent Polymethyl methacrylate, Polyethylene terepthalate(PET), Polytriflouroethylene, the Amino formaldehydes and Polyamides.
- Read – the different types of plastic materials

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- **Drug-Plastic considerations**
  - A packaging system must protect the drug product without in any way altering the composition of the product until the last dose is removed.
  - The following has to be considered in selection of a plastic material:
- ***Permeation***
  - Transmission of gases, vapor or liquids
  - Temperature and humidity will affect permeation

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- ***Leaching***
  - Ingredients of the plastic container may migrate into the formulation
- ***Sorption***
  - This involves removal of constituents of the drug product by the packaging material.
  - This may a serious problem when constituents are in a solution form, and drugs are high potency
  - Chemical structure, pH, the solvent system, concentration, temperature, length and area of contact will affect sorption.

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- ***Chemical reaction***
  - Ingredients of the plastic formulation may chemically interact with components of the drug product.
- ***Modification***
  - The physical and chemical alteration of the plastic package by the drug product.
  - The permeation, sorption and leaching phenomena may alter the properties of the plastic.

Collapsible tubes

Metal collapsible tubes

- Permit controlled amount to be dispensed with good reclosure.
- Provide adequate protection of the product.
- Risk of contamination is minimal
- Light weight and unbreakable
- Lends itself to high-speed automatic filling

- Ductile metals are suitable for collapsible tubes.
  - Tin, Aluminum and Lead are the most common ones.
  - Tin is preferred for pharmaceutical packaging for which purity is the paramount consideration.
  - Tin is the most chemically inert of all collapsible tubes.
  - Aluminum tubes are light in weight and are cost effective.
  - Lead has the lowest cost, but not commonly used for pharmaceutical packaging.

- If a product is not compatible with the bare metal, the interior can be flushed with wax-type formulations or resin solutions.
- Wax linings are most often used with water base products in tin tubes.
- Phenolics, Epoxides, and Vinyls are used with aluminum tubes.
  - These linings give better protection but at a higher cost.
- Phenolics are most effective with acids, and epoxides protect better against alkaline materials.

Plastic collapsible tubes

- Low cost
- Light weight
- Durable
- Pleasant to touch
- Flexible
- Odorless
- Inert
- Unbreakable
- Leak-proof
- Retain shape
- Unique "suck-back" feature – prevent product ooze

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Laminations

- These can solve permeation problems with plastic tubes, and corrosion and breakage problems associated with metal tubes.
- Constructed from several layers of plastic, paper and foil.
- Can be tailored to the product requirements.
- May not provide a satisfactory level of barrier protection for a number of products.

- Some factors to be considered when selecting a liner:
  - Compatibility
  - Appearance
  - Gas/vapor transmission rates
  - Heat resistance
  - Shelf-life
  - Economics

Closures

- Closures are devices by means of which containers can be opened and closed.
- Are the most vulnerable and critical component of a container.
- In evaluating an effective closure system, the major consideration are – the physicochemical properties of the product, and the stability-compatibility requirements.

- An effective closure:
  - Avoid material spilling or volatilization.
  - Allow no substance to enter the container.
  - Avoid contamination from dirt, microorganisms or insects.
  - Avoid deterioration from moisture, oxygen or carbon dioxide.
- Closure can be made from Metals, Plastics, Rubbers or Corks

Types of Closures

- Five basic designs of closures:

1. Screw-on (threaded or lug) cap
2. Crimp-on (crowns) cap
3. Press-on (snap) cap
4. Roll-on cap (Pilfer proof)
5. Friction cap

- Variations of these basic types include:
  - Vacuum
  - Tamperproof
  - Safety
  - Child-resistant
  - Linerless types and
  - Dispenser applications

Screw Cap

Threaded Screw Cap

- The interior of a threaded cap has uninterrupted spiraling threads meant to match with the neck finish of a compatible container.
- Can be made from metal or plastics
- Liners are applied on the inside cap – provide resistance to physicochemical reactions

Lug Screw Cap

- Operates in the same principle as the threaded screw cap type.
- An interrupted thread than a continuous thread is applied.
- Lug caps are compatible with lug-finish containers, which have non-continuous threads.
- Unlike the threaded closure, it requires only a quarter turn.
- Provides a hermetic seal.

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Crown Cap

- Commonly used for beverage bottles

Roll-On closures

- Usually for sealing on to narrow-necked bottles with a threaded neck.
- The unthreaded cap is molded on to the neck of the bottle and forms an air-tight seal.

- Three types of roll-on closures:
  - Resealable
  - Non-resealable and
  - Pilfer-proof closures
- Read - Press-on (snap) cap, and Friction cap closures

Rubber stoppers

- Rubber can be used to make stoppers, cap liners, and bulbs for dropper assemblies.
- The rubber polymers commonly used are natural.
- The types of ingredients commonly found in rubber closures are:
  - Rubber, volcanizing agent, activator, extended filler, reinforced filler, antioxidant, pigment, and waxes.

- Ideal qualities:
  - Satisfactory hardness & elasticity
  - Impermeable to water vapor
  - Resistance to high temperature
  - Resistance to oxidation
  - Rust proof & oil resistance

Cork closures

- Cork is obtained from the bark of oak tree.
- It is chemically inert and it does not impart any odor or flavor.
- It is used rarely because of growth of mold.

Temper Resistant Packaging

- Vulnerability of OTC/non-prescription products to malicious adulteration,
- Public concerns about the safety of drug packaging,
- The main body of Packaging Science effort to combat **intentional adulteration** is focused on tamper-evident (TE) and tamper-resistant (TR).

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- "a tamper-resistant package is one having an **indicator** or barrier, to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred."

- Tamper-resistant packaging may involve immediate container-closure systems or secondary-container/carton systems or any combination.

- The **visual** indication is required to be accompanied by appropriate illustrations or precautionary statements to describe the safeguarding mechanism to the consumer.

XANGO

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- In 1992, the US Food and Drug Administration (FDA) implemented regulatory change in terminology from TR to TE, but TR is still considered as a separate concept by packaging developers.

- To reduce the possibility that the security mechanism can be restored after tampering, the FDA requires either that:

  - The tamper-resistant feature be designed from **materials** that are generally not readily available, or

  - Barriers made from readily obtainable materials carry a distinctive **design** or **logo** that cannot be readily reproduced by an individual attempting to restore the package.

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- Tamper-evident packaging is designed to show a trace, or evidence, such as a torn label or lid, when a product has been tampered.

- Tamper-resistant packaging is designed to resist tampering by including hurdles or barriers that challenge a would-be perpetrator to breach and repair.

- The concept of “tamper-proof” is not used since no package is considered impenetrable.

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- Packaging systems that are capable of meeting the requirements of tamper-resistant packaging:
  - Film wrappers
  - Blister package
  - Strip package
  - Bubble pack
  - Shrink seals and bands
  - Sealed cartons
  - Foil, paper, or plastic pouches
  - Bottle seals
  - Tape seals
  - Breakable caps
  - Sealed tubes
  - Aerosol containers

Symbols used on Packages and Labels

- Many types of symbols for package labeling are nationally and internationally standardized.

- Explosives Flammable liquids Flammable solids Substances liable to combustion Oxidizing substances Toxic substances Corrosives Miscellaneous danger goods

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EXPLOSIVES
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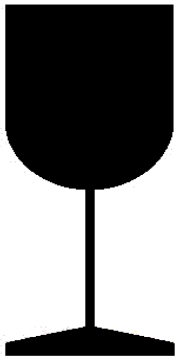
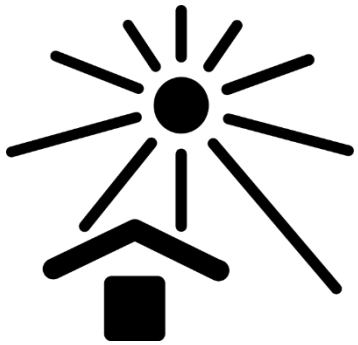
FLAMMABLE LIQUID
3





Labelling and Storage of Pharmaceuticals

- Reading assignment